Clinical Oncology 29 (2017) 26–33

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Irradiating the Subventricular Zone in Glioblastoma Patients: Is there a Case for a Clinical Trial?

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Received 20 April 2016; received in revised form 5 July 2016; accepted 7 July 2016

Abstract

Glioblastoma is the most common and aggressive adult brain tumour. Over the last 10 years it has emerged that the subventricular zone (SVZ), the largest adult neural stem cell niche, has an important role in the disease. Converging evidence has implicated transformation of adult neural stems in gliomagenesis and the permissive stem cell niche in disease recurrence. Concurrently, clinical studies have suggested that SVZ involvement is a negative prognostic marker. It would follow that irradiating the SVZ may improve outcomes in glioblastoma by directly targeting this putative sanctuary site. To investigate this potential strategy, 11 retrospective studies and 1 prospective study examined the relationship between dose to the SVZ and survival outcomes in glioblastoma patients. This review summarises the theoretical underpinning of this strategy, provides a critical evaluation of the existing evidence and discusses the rationale for a clinical trial.

Key words: Cancer stem cells; glioblastoma; neural stem cells; radiotherapy; subventricular zone

Statement of Search Strategies Used and Sources of Information

Computer-guided literature searches were used to identify relevant literature using two independent systems, namely PubMed and Web of Science.

Introduction

Glioblastoma (GBM), the most common and aggressive adult brain tumour, carries a very poor prognosis. This is despite standard of care therapy of maximal surgical resection followed by radiotherapy with concomitant and adjuvant chemotherapy. The poor treatment response, together with the origins, progression and aggressive, inexorable recurrence of this disease, are poorly understood.

There is growing evidence to implicate the subventricular zone (SVZ) in both the initiation and the recurrence of the disease. Preclinical findings, together with a number of retrospective studies correlating high incidental radiation dose to the SVZ with improved survival outcomes, have led to speculation that irradiating the SVZ may be a viable strategy to improve outcomes in GBM. This review will discuss the rationale for a clinical trial, offer a critique of the existing evidence and highlight some important design considerations.

Background

Cancer Stem Cells in Glioblastoma

The cancer stem cell (CSC) hypothesis proposes a cellular hierarchy in which tumours are initiated and propagated by a biologically distinct subpopulation of multipotent cells capable of self-renewal [1]. This is in contrast to the more

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http://dx.doi.org/10.1016/j.clon.2016.09.005
0936-6555/

traditional stochastic model of tumour growth, in which all tumour cells are intrinsically identical and intratumoural heterogeneity is instead due to local microenvironmental influences.

Evidence has emerged over the last decade in support of the CSC hypothesis in GBM. Cells expressing the stem cell marker CD133 have been isolated from human tumours and shown to be capable of transferring a phenocopy of the patient's original disease into mouse models, whereas the CD133-negative cell fraction cannot [2–4]. More recently it has been revealed that neither CD133 nor any other surface marker is an absolute marker of 'stemness' [5,6] and CD133-negative cells cannot only recapitulate tumours in mouse models but also give rise to CD133-positive cells [7]. Indeed, CD133-negative cells are capable of differentiation and this has led to speculation of a hierarchy with CD133-positive tumour-initiating cells giving rise to transit-amplifying CD133-negative cells still capable of disease transference [8]. Moreover, studies have shown that vascular niches [9] and hypoxic conditions [10,11] may induce and maintain CSCs, suggesting a degree of plasticity of CSC phenotype depending on microenvironmental cues [6]. Given the vast inter-patient heterogeneity in GBM, it is unlikely that any single model is universally applicable. Indeed, there is variability in the degree of apparent CSC involvement in different patients, and there are clinical data associating a high CSC fraction in GBM with poor prognosis: both increased stem cell-associated gene expression patterns and increased neurosphere formation *in vitro* are predictors of worse survival [12,13]. The role of stem cells in GBM has been more comprehensively reviewed elsewhere [14].

A Role for the Subventricular Zone in Tumour Initiation?

The origins of these putative CSCs are unclear. A strong possibility is that they are transformed neural stem cells. Indeed, it has been experimentally shown in mouse models that GBM may arise from genomic instability [15] or excessive platelet-derived growth factor (PDGF) signalling [16] in neural stem cells. Thus, neurogenic niches in the brain are candidate sites of transformation. There are two such niches in the adult mammalian brain: the SVZ [17,18] and the subgranular zone (SGZ) in the hippocampus [19]. There is some experimental evidence to support the former as a birthplace of GBM. In p53/NF1-inactivated mouse models, the SVZ is the earliest identifiable site of tumour formation [20]. Further mouse models have shown that tumour suppressor gene deletion in neural stem cells in the SVZ is both necessary and sufficient to induce gliomagenesis, whereas similar targeting of non-neurogenic regions of the brain is not [21]. More recently, phylogenetic reconstruction of tumour evolution revealed that in a proportion of human GBM, the SVZ harbours CSCs that gave rise to the GBM mass, the first direct evidence of a SVZ contribution to human gliomagenesis [22]. However, there are a number of other hypotheses regarding the origin of CSCs in GBM. Gene expression analysis has revealed that in some cases oligodendrocyte progenitor cells distant to the SVZ may give rise to glioma instead [23,24] and a further hypothesis proposes that mature glia dedifferentiate to acquire stem cell-like characteristics [25]. Again, it is plausible that all these hypotheses are correct in different disease subtypes. Thus, it is important to note that neural stem cells have not been definitively established as the single cell of origin in GBM. Indeed, recent results have identified molecular differences between SVZ-originating tumours and cortex-originating tumours, which may drive different behaviours [26].

A Role for the Subventricular Zone in Recurrence?

A complementary idea is that the SVZ contributes to recurrence, even if it is not the original source of the tumour. Mouse models have shown that GBM cells exhibit a tropism for the SVZ, where they acquire a stem cell phenotype and mimic neural precursor cell behaviour by migrating to the olfactory bulb. These cells were shown on transplantation to be highly tumourigenic [27]. A similar SVZ tropism has been suggested in a proportion of human GBM, with the tumour originating outside the SVZ and subsequently growing into it [22]. Additionally, analysis of the pattern of spread of GBM, particularly cases involving the SVZ, reveals that it recapitulates the migration patterns of neural precursor cells [28]. Thus, it is possible that the SVZ can attract and harbour GBM-initiating cells, which then act to drive recurrence both locally and distantly through the same migratory routes as neural precursor cells.

Despite uncertainty over its precise role, there is a substantial body of literature to suggest that the SVZ plays a clinically important role in at least a proportion of GBM. SVZ-contacting tumours have repeatedly been shown to be associated with more aggressive clinical behaviour, such as multifocality and distant recurrences [29–32] (albeit not universally [33]) as well as robustly associated with worse prognosis [26,31,34,35]. Recent results have shown that SVZ-involving tumours have increased blood volume in the non-enhancing lesion than cortex-involving tumours, potentially attributing poor survival to an aggressive vascular phenotype [26]. Additionally, it has recently been shown that both SVZ-contacting and non-contacting tumours have a propensity to recur near to the SVZ or the SGZ [32], further suggesting that neurogenic regions may be reservoirs of subclinical disease, which then drives recurrence (Figure 1).

Relevance to Radiation Therapy Treatment Planning

Traditionally, generous margins have been added to the gross tumour volume during radiotherapy treatment planning to allow for sub-clinical tumour infiltration into adjacent brain (Figure 2). A 2–3 cm margin for clinical target volume (CTV) is informed from radiological and pathological observations of disease recurrence [36]. Patterns of failure studies confirm that with such CTV margins, the pattern of failure is predominantly local, both with single modality radiation therapy and combined chemoradiation treatment [37,38]. Local failure patterns suggest that in